REMARKS

Claims 49-52, 56-60, 64 and 68-83 are pending. Claims 49 and 57 have been amended. Support for the amendment can be found throughout the application as filed. Support for the amendment directed to incorporating substrates, products and stoichiometry into a stoichiometric matrix, can be found, for example, in the claims as originally filed, at page 8, line 11 through page 9, line 17, Example 1 and Figure 2. Support for the amendment directed to a metabolic capability of the *in silico* strain that is predictive of the microbe's phenotype, can be found at, for example, page 5, lines 9-11 and 15-17; page 13, lines 14-18; page 16, lines 4-6 and 8-9; page 17, lines 19-27 and Examples 3 and 4. Accordingly the amendments do not introduce new matter and entry thereof is respectfully requested.

Interview Summary

Applicant, representatives from Applicant's licensee Genomatica and counsel of record wish to thank Examiners Negin and Moran for the telephonic interview conducted on April 29, 2009. Applicant, counsel and licensee's representatives discussed that one skilled in the art would not have combined the references cited under 35 U.S.C. § 103(a) to arrive at the claimed invention because the alleged motivation to do so is lacking. A proposed declaration directed to this point was discussed.

Rejections Under 35 U.S.C. § 103

Claims 49-52, 56-60 and 68-83 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Pramanik et al., *Biotech. and Bioengineering* 56:398-421 (1997) in view of Blattner et al., *Science* 277:1453-69 (1997) and Kunst et al., *Rev. in Microbiol.* 142:905-12 (1991). The Examiner alleges that Pramanik et al. investigate a stoichiometric model of *E. coli* metabolism. The Examiner concedes that Pramanik et al. fail to teach obtaining a plurality of DNA sequences and determining which open reading frames correspond to metabolic genes. Blattner et al. allegedly describes mapping the *E. coli* genome and assigning function to proteins by determining similarity to proteins of known function. The Examiner concedes that neither Pramanik et al. or Blattner et al. teach assigning function to genes of unknown function based on homology to proteins in a different organism. Kunst et al. is alleged to describe sequencing of *B.*

substilis genome and express an interest in comparing the *B. substilis* and *E. coli* genomes. The Examiner concludes that it would have been obvious to one of ordinary skill in the art to modify the stoichiometric model of Pramanik et al. by using the complete genome sequence of Blattner et al. and the genome comparisons of Kunst et al. because (1) metabolism can be further analyzed; (2) the full sequence enables global approaches to understanding biological function and looking at the evolutionary history, and (3) homology comparisons allow for an analysis of evolutionary differences.

The Supreme Court in *KSR* stated that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l. Co. v. Teleflex, Inc., et al.*, 127 S. Ct. 1727 (2007). The Supreme Court noted that inventions in most, if not all, instances rely upon building blocks "long since uncovered." Thus, claimed discoveries will generally be combinations of what is already known. *KSR* requires that an Examiner provide "some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *Id.* at 1741. An Examiner must "identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does," *Id.* Furthermore, the Examiner must include an explanation of "the effects of demands known to the design community or present in the marketplace" and "the background knowledge possessed by a person having ordinary skill in the art." *Id.* It is respectfully submitted that the current Office Action falls short of providing the analysis described by the Supreme Court in *KSR*.

Applicant submits that the conclusory statements put forth in the Office Action that it would have been obvious to modify the stoichiometric model of *E. coli* as described by Pramanik et al. with the genome sequence of Blattner et al. and the homology comparisons of Kunst et al. allegedly because (1) metabolism can be further analyzed; (2) the full sequence enables global approaches to understanding biological function and looking at the evolutionary history, and (3) homology comparisons allow for an analysis of evolutionary differences fail to include the requisite explanations required by *KSR*. For example, the required explanations of the effects of demands known to the design community or present in the marketplace and the background knowledge possessed by a person having ordinary skill in the art are lacking. Accordingly, the Examiner has failed to articulate a *prima facie* case identifying a reason that would have

prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does.

In its discussion of *United States v. Adams*, 383 U.S. 39, 40 (1966), the Court in *KSR* further indicated that the presence of unexpected results supports conclusions that the invention is not obvious to those skilled in the art. *KSR v. Teleflex*, 127 S.Ct. at 1740.

Applicant respectfully submits that the skilled person would not have modified the stoichiometric model of Pramanik et al. with the genome sequence of Blattner et al. using the comparisons of Kunst et al. to determine functions of unknown proteins based on the motivation stated in the Office Action, or any other motivation in the knowledge of one of ordinary skill in the art or from the nature of the problem to be solved.

As set forth previously of record, Pramanik et al. describe construction of a metabolic model using only biochemical data. While Pramanik et al. list some genes, the list is incomplete compared to the model and consists only of known genes encoding proteins with a known biochemical activity. There is no teaching, suggestion or hint of an incentive to use information other than know biochemical data, including gene or genomic information, to modify or expand the content of the model. Rather, Pramanik et al. state "[t]here was close agreement between the predicted and experimentally determined flux values" (page 410, col. 1, para. 3) and "[t]his metabolic model should be a useful tool for studying the effects of reengineering pathways" (page 410, col. 2, para. 2). Based on these statements, one skilled in the art would conclude that the Pramanik et al. model is successful and that there is no problem to be solved that would benefit by including metabolic reactions deduced from open reading frames of genes of unknown function.

Blattner et al. report on the *E. coli* genome sequencing and similarly fail to provide any teaching, suggestion or motivation to combine genome sequence information with the biochemically-based model of Pramanik et al. Nor does the genome sequence described by Blattner et al. provide any general knowledge that would contain an incentive to motivate one skilled in the art to incorporate the described genomic information into a stoichiometric model because a function or homology match can not be assigned to a sizeable fraction of the genes. For example, Blattner et al. teach that 38% of the protein-coding genes have no attributable

function (abstract, lines 1-2; page 1458, col. 3, para. 1, lines 1-9, and Table 4) and that nearly 60% of *E. coli* proteins have no match in any other complete genome that was considered (page 1459, col. 2, para. 2, lines 1-3).

Kunst et al. also fails to cure the deficiencies or provide any incentive to utilize open reading frames of genes of unknown function in a stoichiometric model because Kunst et al. admits that the majority of genes will have an unknown function.

> At the first level of analysis, the DNA sequence will lead to a complete catalogue of putative protein sequences. These are likely to fall into one of 3 categories: (1) those whose functions are known, (2) those which show similarities with proteins identified in other organisms and which may have similar though not necessarily identical function in *B. subtilis*, and (3) those, probably the majority, whose function is unknown at present.

Id., page 205, para. bridging columns 1 and 2 (emphasis added).

A teaching that a majority of genes will have an unknown function fails to provide any incentive or motivation for one to combine Pramanik et al. and Blattner et al. with Kunst et al. because it informs the skilled person in the art that there is a high likelihood that incorrect information will be incorporated into the model. Incorrect assignment and incorporation into a stoichiometric model of putative metabolic genes or genes with unknown function as a metabolic gene will lead to inaccurate fluxes and diminution in the ability of the model to correctly simulate or predict a phenotype of the microbial organism. Accordingly, both Blattner et al. and Kunst et al., while they report on sequenced genomes and comparative analysis, teach that one skilled in the art, upon a careful reading of Pramanik et al., Blattner et al. and Kunst et al., would not be motivated to combine these references to arrive at the invention as claimed because incorporation of incorrect information leading to a less predictive model is a likely possibility.

Applicants submit herewith three Declarations by Drs. Keasling, Palsson and Nielsen, attached as Exhibits A, B and C, respectively. Dr. Keasling is the senior author on the primary reference cited above and a leader in metabolic modeling. Dr. Palsson is the inventor on the above-identified application and a pioneer in the field of stoichiometric models of metabolism. Dr. Nielsen is a prominent researcher in the field of metabolic models. Drs. Keasling and Palsson declare that one would not have expected the combination to result in a model that is

capable of accurately predicting a microbial phenotype. Dr. Palsson further declares that a prominent scientist in the field wrote a letter to him stating his disbelief that a stoichiometric model constructed primarily from genomic information would be expected to work. Dr. Nielsen declares that the prominent scientist also voiced his disbelief in a public forum.

Dr. Keasling declares that at the time when the genome sequence of Blattner et al. was available, he did not consider utilizing sequence information to incorporate additional metabolic reactions into his model because the resulting *in silico* model would not have been expected to be predictive of an actual organism's metabolism, ¶7. Dr. Keasling further declares that his model, as described in Pramanik et al., would have been expected to produce a large number of inaccurate fluxes and lead to a model that is much less predictable if putative reactions were included based sequence homology comparisons, ¶7. Dr. Keasling also declares that identification and assignment of some open reading frames as putative metabolic enzymes was speculative and likely to result in incorporation of inaccurate information and loss of the resultant model's ability to predict a phenotype, ¶8. The ability of a model constructed from genomic sequence data to predict actual cellular metabolism was unexpected (¶¶ 7 and 8).

Dr. Palsson declares that those skilled in the field of metabolic modeling and engineering would not have been motivated to incorporate the genomic data of Blattner et al. or sequence comparisons of Kunst et al. because the predictability of the resultant model would have been expected to be reduced due to incorporation of incorrect information, ¶¶ 8-9. Dr. Palsson further declares that Dr. Bailey, a respected and prominent scientist in the art, did not believe that the construction of a metabolic model from genomic sequence information worked as claimed. However, if such model did work as claimed and provided predictable fluxes, the approach represents a very major advance, ¶11. This disbelief or alternative characterization as a breakthrough discovery is supported in a letter sent from Dr. Bailey to Dr. Palsson where Dr. Bailey expressly states that the model as claimed is difficult to believe, or alternatively, a breakthrough in the field, ¶¶13-16.

Dr. Nielsen declares from personal knowledge that Dr. Bailey publically opposed Dr. Palsson by voicing his belief that it was not possible to predict metabolic functions and cellular

physiology using stoichiometric models reconstructed from genomic information because the large degrees of freedom are likely to yield to false phenotypes, ¶8.

Based on the attached Declarations and the accompanying remarks herein, Applicant respectfully submits that the cited references do not provide any suggestion or motivation to combine their teachings to arrive at the claimed invention. Nor do the cited references, determined from the vantage point of one skilled in the art, including their general knowledge and knowledge of the problem to be solved, provide any incentive that would have motivated one skilled in the art to modify the references or combine them to arrive at the invention as claimed.

Claim 64 stands rejected under 35 U.S.C. § 103(a) as allegedly obvious over Pramanik et al. in view of Blattner et al., in view of Kunst et al. and further in view of Xie et al., *TIBECH* 15:109-113 (1997). Pramanik et al., Blattner et al. and Kunst et al. are applied as described above. Xie et al. allegedly describes integrated approaches to the design of media and that the composition of growth medium and its depletion over time affects growth of cells. The Examiner alleges that it would have been obvious to one of ordinary skill in the art to modify the studies of *E. coli* of Pramanik et al., Blattner et al. and Kunst et al. by the nutrient depletion studies of Xie et al. because stronger media can be designed to enable better growth of cells.

The rejection of claim 64 relies on the primary reference by Pramanik et al. in combination with Blattner et al. and Kunst et al. The deficiencies of this combination are detailed above and in the attached Declarations. The tertiary reference to Xie et al. does not address, much less cure these deficiencies, which are fatal to the instant obviousness rejection. Accordingly, Applicants respectfully request withdrawal of the rejection of claim 64 under 35 U.S.C. § 103 as obvious over Pramanik et al. in view of Blattner et al. and Kunst et al. as applied to claims 49-52, 56-60 and 68-83, and further in view of Xie et al.

Double Patenting

Claims 49-52, 56-60 and 64 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly obvious over claims 26-28, 30, 32,

35, 36, and 39-41 of copending application serial No. 11/980,199. The Examiner points out that Applicant's previous arguments are moot in view of the new ground of rejection.

Applicant respectfully requests deferral of this provisional ground of rejection until such time that there is an indication of allowable subject matter. Applicant respectfully points out that application serial No. 11/980,199 has yet to receive any substantive prosecution. Per Applicant's previous response, should the subject application be deemed in conditions of allowance prior to application serial No. 11/980,199, Applicant respectfully requests that this provisional rejection be withdrawn in this earlier filed application and permit it to proceed to issuance without need of a terminal disclaimer. MPEP § 804(I)(B).

CONCLUSION

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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